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A CONTRIBUTION TO THE PATHOLOGY OF REFRIGERATION FACIAL PALSY.

BY L. PIERCE CLARK, M.D.,

VISITING NEUROLOGIST TO THE RANDALL'S ISLAND HOSPITALS AND SCHOOLS; CONSULTING NEUROLOGIST TO THE MANHATTAN STATE HOSPITAL, NEW YORK, AND THE CRAIG COLONY FOR EPILEPTICS, SONYEA, NEW YORK; ASSISTANT NEUROLOGIST TO THE VANDERBILT CLINIC (COLUMBIA UNIVERSITY), NEW YORK.

IN order that the pathogenesis of Bell's palsy may be definitely determined we must insist that the type of cases studied shall be uniform in clinical occurrence and symptoms. Bell's palsy *per se* is a refrigeration palsy occurring in individuals who have no other organic disease. This statement, however, must not rule out such chronic predisposing diseases as rheumatism. In the refrigeration Bell's palsy a rheumatic history may or may not be present; it is much oftener absent. In the Vanderbilt Clinic statistics it was ten times more frequently absent than present.

The cause of the great frequency of paralysis of the facial nerve, as in Bell's type of palsy, is still moot. It is, however, due probably to anatomical causes. The nerve has a tortuous and exposed course through the Fallopian canal. It is easy to understand that inflammation may readily extend from the middle ear, or that cold may operate through the same channel, causing a local neuritis and palsy. In further substantiation of the vulnerability of the facial nerve to exposure, we know the facial nerve is infrequently paralyzed when the face is properly protected by hair or clothing. Bell's palsy is very infrequently seen in animals. Furthermore, it is reasonable to suppose that a certain number of individuals suffer a congenital narrowing of the foramen or canal through which the nerve passes. It is known that the size of the foramen of the two sides differs in the same person and in different persons. Inasmuch as facial palsy occurs much more frequently in man than in animals, one is justified in assuming that the greater functional and structural development of the nerve in man is a factor in the frequent causation of the nerve palsy. It is also worthy of note in comparative anatomy that the soft tissues increase more rapidly in size than the bony parts in the process of evolution. This would explain why the facial nerve is often found very closely enveloped in its bony canal. Thus it is easy to account for the relative frequency with which the initial swelling of inflammation in the facial nerve (Fallopian neuritis) may induce secondary compression of the nerve strands in a rigid bony canal, and finally cause thereby a simple degeneration of the whole peripheral segment. This theory would explain the varying grades of completeness of palsy following a variation of the exciting cause.

No cases of refrigeration Bell's palsy have been studied pathologically to the time of this report. Before placing the results of a study of two such cases on record, a critical digest of the few cases which are often quoted to explain the pathology of Bell's palsy need to be disposed of: three cases figure extensively in literature—those of Minkowski,[1] Dejerine and Theohari,[2] and Alexander.[3] The findings in all are quite unreliable, as the examinations were made in all three some fourteen years ago, at a time when the distinction between the histological changes of inflammation and degeneration of peripheral nerves were not so definite as they are today. Indeed, many changes were then described as inflammatory which are known today to be only degenerative. Much confusion also resulted owing to imperfection of staining methods. The acceptance today of these earlier findings accounts in no small degree for the contradictory beliefs since held in regard to the initial lesions in all morbid processes of peripheral nerves.

The foregoing facts account in part for the hesitancy with which one accepts the purely degenerative changes noted in the Fallopian canal of Minkowski's case, as he expressly states that the cellular elements showed no changes that might be interpreted as inflammatory. He could hardly have overlooked the leukocytic and connective-tissue cell invasion seen in simple degeneration of divided nerves, which but a very few years ago were counted as inflammatory. These changes, although now known to be as common in inflammation as in degeneration, are nevertheless of a passive character. One must not only designate Minkowski's observations as inexact in analysis of the histological lesion, but also discredit the acceptance of the case at all, as his patient died from acute poisoning two months

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[1] Arch. f. Psychiatrie, 1891, xxiii.

[2] Cited by Minkowski from Compt.-rend. Soc. de biol. (reference omitted).

[3] Arch. f. Psychiatrie, 1901-2, xxxv, 783, and Arch. f. Ohrenheilk., 1904, lxii. 8.

after the supervention of palsy, a time at which distinct deposit of connective-tissue infiltration must have been unmistakably present. The faults in Minkowski's observations also prevent us from considering the case as in accord with the view of a degenerative neuritis or simple degeneration in the segment of the nerve anterior to the Fallopian canal, although he expressly defines a simple degeneration of the nerve in the periphery. The cellular changes were reported to be also progressively less as he proceeded centrally (evidence of non-regeneration). The degeneration was traced as far as the geniculate ganglion. The ganglion itself and the nerve above were, however, reported normal. We may, therefore, conclude definitely to exclude Minkowski's findings as a case of Bell's palsy with simple degeneration, as he does not appear to have given any attention to the state of the vascular perineural sheath, in which the most marked changes occur in inflamed nerves. The microscopic findings are certainly unique and unexplainable upon any basis for Bell's palsy as we know the lesion. One may also state in passing that the absence of nerve swelling in the canal may be explained on the ground that the examination was made more than two months after the initial neuritis, which is a sufficient time for the nerve swelling to have disappeared completely, had it once been present.

The facial palsy studied by Dejerine and Theohari occurred in a woman of eighty-one with uterine cancer—a complication which might easily vitiate its inclusion, in view of the fact that the palsy was preceded by a superficial cervical zoster, a condition now well known to be an infectious lesion of the posterior nerve ganglion. Further to complicate the clinical picture the woman died of an infectious pneumonia. While the condition of palsy of the facial nerve might in result be analogous to Bell's so-called refrigeration palsy, the lesion, as we shall note, must have been quite different. The findings in Dejerine and Theohari's case showed that the nerve was not compressed in the petrous bone, but that the entire facial nerve was the seat of parenchymatous neuritis, especially marked in the branches to the chin and the lower lip. A few degenerated fibers were found also in the chorda tympani. But few fibers of the nerve within the petrous bone were diseased, and the nerve roots were nearly intact. Many hyaline cells were found in the facial nucleus, and there was an absence of chromatin; the nucleus was nearly destroyed by disease. The case can hardly be considered in any light other than one of infectious neuritis of the whole peripheral system—nerve endings, trunk, root, and nucleus. The clinical and pathological state indicates conclusively that it was not one of refrigeration Bell's palsy, and the findings cannot explain the pathogenesis of Bell's palsy.

In comparing Alexander's case, on the one hand, with the cases of Minkowski or Dejerine and Theohari, we are struck with the essential difference in the anatomical changes in the two classes of cases. Alexander's occurred in a man aged fifty-six, who also suffered from cancer, but of the œsophagus. The intercurrent Bell's palsy underwent partial recovery in the four weeks preceding death by cancerous cachexia. A degenerative inflammation of the facial nerve and geniculate ganglion was found; the entire periphery was affected by degeneration. All the inflammatory changes were restricted to the nerve in the Fallopian canal and geniculate ganglion. The contiguous structures showed no change. Alexander makes no mention of examination of nerve roots or nucleus. Some doubt must be thrown upon the value of Alexander's case in interpreting the pathology of Bell's palsy, as the cause inducing the facial palsy probably was an infection from the cancer lesion (infectious facial neuritis).

Assuming Bell's palsy to be refrigeration palsy, one must discard all the nerve findings heretofore reported as such, as well as some six other cases studied in suppurative and necrotic mastoiditis attended or followed by seventh-nerve palsy. For the purpose of this paper a detailed analysis of the latter class is omitted, for obvious reasons.[4]

Probably few will deny that in the pure refrigeration palsy cases there is any evidence that cold ever paralyzes intramuscular nerve endings. It is certain, moreover, that paralysis of all the fibers in a nerve, and of no other fibers in the immediate neighborhood, is an index of nerve-trunk disease. There is no evidence on record that the trunk of the facial nerve is involved in inflammation after its emergence from the canal. While we tentatively accept the lesion of refrigeration facial palsy to be one of Fallopian neuritis, it must be admitted that this lesion is still unproved. This latter statement, however, does hold true for the condition of the trunk after emergence from the canal, as the two cases about to be reported as evidence testify. Further corroborative data must also soon be forthcoming as the surgical treatment of Bell's palsy by nerve anastomosis is more generally practised.

The summary of findings in two such cases of refrigeration palsy treated by faciohypoglossal anastomosis (operation by Dr. Taylor) is given as a preliminary contribution to the final disposition of the exact lesion in the peripheral trunk of the facial nerve of this type of palsy.

The palsy in the first case was typical refrigeration palsy of the right side. The paralysis was complete. There was no family or personal history of rheumatism or syphilitic taint. The woman in whom it occurred was forty-five years old. Reactions of degeneration remained complete, and *at the end of four months* faciohypoglossal nerve anastomosis was undertaken successfully. A small portion of the trunk of the facial nerve just below the stylomastoid foramen was preserved for microscopic study.[5]

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[4] The secondary neuritis of the facial nerve following mastoiditis, which has been so carefully described by May (Münch. med. Woch., 1884, No. 31), Darkschewitch and Tichonow (Neurol. Ctbl., 1893, x, 329), Flatau (ibid., 1896, xv, 718), and Meyer (Jour. Exper. Med., Nov., 1897), is quite different in onset, course, and pathology from that seen in Bell's refrigeration palsy. The lesion is much more severe and extensive. It is a parenchymatous (infective) neuritis, and its much graver prognosis is in marked contrast to Bell's palsy.

The second case of left facial palsy was also a typical refrigeration Bell's palsy. It occurred in a woman of forty-two, who was otherwise well. There was no rheumatic or syphilitic taint in the family or personal history. *In the twelve years following the onset* of the palsy no functional regeneration was noticed. On the other hand, there was complete atrophy of all the muscles supplied by the facial nerve above the angle of the mouth. Those at and below the angle of the mouth underwent considerable atrophy and contracture.

There was no spasm of muscle in these parts. Complete reactions of degeneration were obtained. The operation of faciohypoglossal anastomosis was undertaken by Dr. Taylor to correct the deformity of the lower part of the face, and to restore as much functional power as possible in these parts. The portion of the nerve trunk examined was taken in the same manner and from the same place as that of Case I.

A summary of the findings in the two cases is as follows: The two cases presented the condition found in a more or less acute and chronic state, respectively. In Case I (acute) the nerve trunk was in a condition of incomplete degeneration (Fig. 1). There were still a few nerve fibers undegenerated, or in which the myelin sheath was only partially broken up, and these stood out in marked contrast to the degenerated nerve fibers in which they were embedded, which latter show here and there fragments of myelin. There was, furthermore, a marked invasion of the tissues with leukocytes, and the cells of the neurilemma were shrunken and shrivelled in some portions; in others the nuclei of the neurilemma cells were large and were defined. The perineural sheath showed marked infiltration with leukocytes. The pathological picture shown was one of simple degeneration, with here and there slight evidences of a reparative process, like those shown most exquisitely in the recent exhaustive experimental studies by Ballance and Stewart.[6]

The picture in Case II (chronic) was in marked contrast to the preceding (Fig. 2). The nerve fibers were completely degenerated, showing but occasional granules belonging to the myelin sheath. There were no undegenerated fibers. The perineural sheath showed the most decided change. There was marked proliferation of the cells belonging to the perineural sheath, with infiltration of the tissues with clumps of cells scattered here and there throughout the section. This tissue exceeded the proper nervous tissue of the section by about two to one. The neurilemma cells were markedly shrunken and shrivelled. The picture, again, was one of complete degeneration, with no evidence of a repair process. If autogenous

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[5] The microscopic analysis of my two cases here reported was made by Dr. Thomas P. Prout, to whom my thanks are due for the report and the photomicrographs.

[6] The Healing of Nerves.

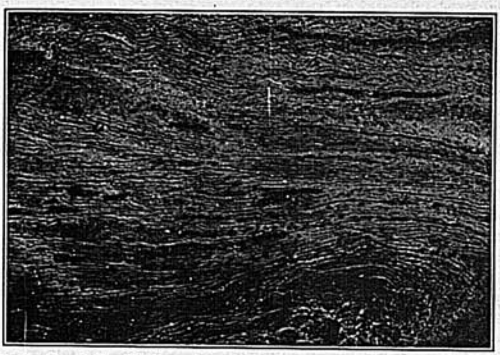

Fig. 1.—Case I, Mrs. B. G., aged forty-five years; acute refrigeration (Bell's palsy) of four months' duration. Photomicrograph of the facial nerve at the stylomastoid foramen, showing simple degeneration of the nerve fibers; here and there are seen neurilemma cells and a few regenerating nerve fibers, but no evidence of inflammatory lesion in the nerve. Peripheral degeneration following Fallopian (compression) neuritis.

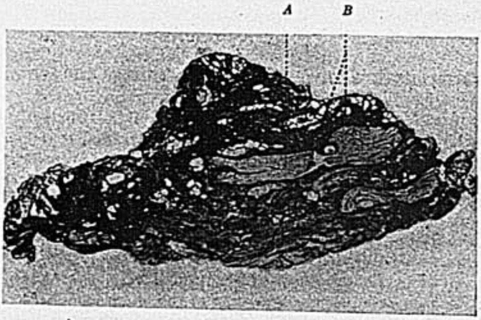

Fig. 2.—Case II, Mrs. M. J., aged forty-two years; chronic refrigeration (Bell's) palsy of twelve years' duration. No functional regeneration. Great atrophy and contracture of the muscles. Photomicrograph of the facial nerve at the stylomastoid foramen, showing simple degeneration of the nerve and connective tissue overgrowth. No attempt at repair. *A*, nerve fibers; *B*, connective tissues. No evidence of an inflammatory lesion. Simple peripheral degeneration following Fallopian (compression) neuritis.

peripheral regeneration (embryonic) had taken place in this case it must have disappeared, as no evidence of such was present in the specimen.

From a clinical viewpoint many data point to a simple degeneration of the peripheral portion of the facial nerve in Bell's palsy. The infrequency of pain[7] in the peripheral nerve distribution and the absence of tenderness upon pressure in either the nerve or the muscles indicate degeneration. Again, the passive movements of the muscles are not painful, as in neuritis. Certainly there are as few clinical as well as pathological reasons to indicate that the lesion in the peripheral portion of the nerve in Bell's palsy is one of parenchymatous neuritis. The clinical phases of recovery in refrigeration palsy of the facial nerve have many points in common with those seen in reunited or severely compressed peripheral nerves occurring elsewhere in the body.

Finally, I may summarize this study by saying: (1) Refrigeration Bell's palsy is in all likelihood a Fallopian neuritis; (2) the strands of the facial nerve are severely compressed by the initial inflammatory swelling in a rigid canal, and in this manner degeneration of the whole periphery of the nerve is induced; (3) the predisposition of some individuals to a Fallopian neuritis, and its consequent facial palsy, rests largely on anatomical grounds, which are mainly comprised in the fact that the nerve has a tortuous and exposed course through a bony canal, probably often congenitally insufficient in size.

THE CHANGES PRODUCED IN THE KIDNEYS BY RÖNTGEN IRRADIATION.

BY ALDRED SCOTT WARTHIN, M.D., PH.D.,
PROFESSOR OF PATHOLOGY, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICHIGAN.

THE publication during the last two years of Heineke's important work upon the changes produced in the lymphoid tissues by Röntgen irradiation and the observations of Albers-Schönberg upon the disturbances of testicular function similarly produced, have effectually disposed of the dictum that had been rather vigorously upheld that Röntgen-rays produce changes only in the superficial parts of the body exposed to their action. While other investigators have confirmed the observations of these writers and have added to our knowledge concerning the changes in the lymphoid tissues and sexual glands, we are still practically ignorant of the effects of Röntgen irradiation upon the other internal organs. The few investigations made along these lines have been rather of the nature of casual or incidental observations, and do not lead us to any definite conclusions. Particularly with reference to renal changes due to Röntgen irradiation, are we still in the dark, and no thorough investigations have been carried out in this field. In fact, but two observations relating to this subject are to be found in the literature, those of Linser and Baermann and Buschke and Schmidt.

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[7] Pain when present is usually confined to the ear or its immediate neighborhood (probably due to the compression neuritis in the bony canal).

Linser and Baermann[1] found that exposures of one hour produced transitory albuminuria without apparent changes in the renal epithelium. Buschke and Schmidt[2] could discover no disturbances of function or pathological changes in the kidneys of guinea-pigs and rabbits exposed percutaneously for periods varying from five minutes to two hours, although some of the animals died without any apparent cause during the first week after the exposure. In animals in which the kidneys were laid bare by incision and freed from their fatty capsules, irradiation with a medium tube for from one-half to two hours produced in some cases a slight albuminuria during the first week. In two cases only were definite histological changes found, the animals dying without apparent cause forty-five and fifty-six days respectively after the irradiation. In the kidneys of these animals extensive necrosis of the cortical substance was found, the necrosis extending even into the medullary pyramids. The neighboring tissues showed a marked reactive inflammation. Other animals similarly exposed lived six to eight weeks, showing when killed neither macroscopic nor microscopic changes in the irradiated kidney.

From these somewhat unsatisfactory and inconclusive experiments Buschke and Schmidt conclude that the kidney epithelium is much more resistant to the action of Röntgen rays than is the epithelium of the testicles. Based upon this comparison they advance the view that cells capable of speedy regeneration are less resistant to the rays, while those more slowly regenerating offer a greater resistance. Since the experiments of Linser and Baermann were practically negative in so far as the production of histological changes in the kidneys was concerned, and as only two of the animals used by Buschke and Schmidt showed pathological changes (and these changes might well be the result of the operative manipulations), it will be seen that at the present time there is practically no conclusive proof that renal changes can be produced by Röntgen irradiation. Clinical observations have been made of the occurrence of nephritis after irradiation, but the anatomical changes are unknown.

I was led to the present investigation by the remarkable kidney changes discovered in the material from two cases of leukemia that had been treated for some time with Röntgen rays. The first of these cases was a patient of Drs. Brown and Jack, of Decatur, Illinois. The leukemia was of the myeloid type, the white cells numbering 800,000, and the spleen being greatly enlarged. Röntgen irradiation of the splenic region twice a week for two months produced a great improvement, the spleen becoming reduced in size and the number of white cells diminished. Daily exposures were then made for seven months, and the improvement was so marked that hopes of a complete cure were entertained. The patient remained in relatively good condition for six months although the leukocyte count was high and there was a high percentage of myelocytes. Röntgen irradiation was renewed when there was a change for the worse. The treatment was then continued for seven weeks, but the man gradually grew worse and died with symptoms of a severe intoxication. The autopsy was performed by Dr. Jack, and the material sent to me for examination. It had been fixed in 4 per cent. formaldehyde solution, and was embedded in paraffin and stained with various stains.

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[1] Fortschritte aus dem Gebiete der Röntgenstrahlen, December 9, 1904.

[2] Deut. med. Woch., 1905, xxi, 495.

Microscopic examination of sections of the lungs, liver, pancreas, and large and small intestine showed atrophy, chronic passive congestion, and slight parenchymatous degeneration, but no signs of a leukemic condition. The white cells in the bloodvessels were not increased and there were no leukemic infiltrations. The spleen did not present the characteristics of a leukemic organ. Only in the retroperitoneal lymph nodes were changes found suggestive of an intrinsic disease of the blood-cell forming organs. These nodes showed a marked lymphoid hyperplasia, the normal structure of a lymph node being wholly lost. The lymphoid cells infiltrated the capsule and the surrounding adipose tissue. In so far as the pathological picture was concerned the leukemic condition had been changed into an aleukemic condition.

Without considering the other pathological features of this case, certain remarkable changes in the kidneys demand our attention at the present time. On cutting the kidney into pieces suitable for embedding, marked grating and resistance were noted. The cut surface showed numerous whitish areas and stripes corresponding chiefly to the medullary rays in the cortex and the collecting tubules in the medullary pyramids. The sections were cut with great difficulty owing to the resistance offered by these whitish areas. When stained the sections showed the presence of extensive deposits of lime-salts filling up the tubules and replacing the renal epithelium (Figs. 1 and 2). The deposits stained deep violet with hematoxylin, and dissolved slowly in 1 per cent. hydrochloric acid without the formation of bubbles. Although found chiefly in the distal convoluted tubules and in the straight tubules, the deposit was present also in many of the proximal portions of the convoluted tubules and glomeruli. The remaining portions of the parenchyma were atrophic and presented more or less marked cloudy swelling and fatty degeneration.

When dissolved out the lime-salts left behind a granular albuminous detritus, the renal epithelium of the affected tubules being completely necrosed.

In a second case of leukemia treated by Röntgen rays similar deposits of lime-salts were found in the kidneys. The patient, from Dr. Dock's clinic, University Hospital, presented universal glandular enlargement with a blood picture of a small-cell lymphatic leukemia. Thirty treatments in all of ten-minute exposures with a medium tube, six to eight inches distance, were given every other day to the cervical and axillary regions. The inguinal regions received nineteen treatments. The enlarged glands became much reduced in size, and there was at first a decrease in the number of leukocytes, followed later by a rise. While the general condition seemed at first somewhat improved, the patient soon grew worse and died rather suddenly with symptoms of intoxication. The autopsy was performed by me. Considering here only the kidneys, they were enlarged, pale, and soft. On section the straight tubules of the medullary pyramids appeared as whitish streaks and spots that could be scraped away as a finely granular chalky substance having a distinctly gritty feel. On microscopic examination the renal epithelium showed slight degenerative changes and there was local inflammatory reaction. Cloudy swelling and fatty degeneration were most marked in the distal portions of the convoluted tubules and in the straight tubules, the lumina of many of these being filled with casts of a finely granular calcium phosphate that, dissolved out with acid, left a granular albuminous cast. In all respects the condition resembled that seen in the first case, but much less advanced.

The extensive renal degeneration and calcification found in these two cases of leukemia, treated by Röntgen rays, excited at once interest in the question as to the possibility of some relation between these changes and the treatment. That such changes may be found in cases of leukemia not treated by irradiation does not appear in the literature. I have also examined the kidneys from twenty-five cases of leukemia (myeloid, small and large-cell lymphatic, chloroma, and the leukemic forms of lymphocytoma). In all these more or less extensive parenchymatous degeneration was found in the kidneys, as well as leukemic metastases, localized inflammatory changes, etc., but in none was there any deposit of lime-salts seen or such extensive necrosis. In general it may be said that the amount of parenchymatous degeneration found in the kidneys of leukemic cases is in direct proportion to the number of degenerating white cells seen in the blood, spleen, bone-marrow, and lymph nodes of a given case. The most extensive renal changes were found in two cases characterized by marked leukolysis.

The relationship apparently existing between the renal changes and leukocyte destruction, as shown by a study of these twenty-five cases, may be taken as an evidence that the more severe renal changes in the two cases of irradiated leukemia are the results of some poison arising from the excessive destruction of white cells by the x-rays. This view is supported by the pathological findings in a third case of leukemia treated by Röntgen rays. A patient of Drs. Grosh and Stone, of Toledo, Ohio, had myeloid leukemia for two years, the white cells being 226,500, and the spleen showing the usual enlargement. He was given five-minute exposures with a medium tube at a distance of six to eight inches for six weeks. The white cells were reduced to 10,600; the myelocytes from 52 per cent. to 2 per cent., and the spleen became smaller. The patient then died suddenly with signs of a severe intoxication. The various organs presented the picture of a myeloid leukemia with excessive leukolysis. The spleen in particular showed great numbers of disintegrating white cells and numerous areas of complete necrosis. The renal epithelium presented the appearances of advanced cloudy swelling, fatty degeneration, and simple necrosis. The bloodvessels were much congested. No deposits of lime-salts were present. The collecting tubules contained numerous hyaline and granular casts.

As it seemed very probable that the extensive kidney lesions in these three cases of irradiated leukemia bore some definite relation to the treatment and the resulting destruction of white cells, it was determined to carry out some experimental work bearing upon this point. The results are given below.

EXPERIMENTAL INVESTIGATIONS. *Technique.* The animals used were white mice and rats, guinea-pigs, rabbits, and Belgian hares. Percutaneous exposures were given, since all other sources of damage to the kidneys were to be eliminated, and it was also desirable to compare the percutaneous effects of the rays upon the kidneys with those upon the lymphoid tissues. The small animals were placed wholly in the field of exposure, while in the larger ones the field of irradiation was limited to the abdominal region including the spleen and kidneys. A medium soft tube was used, distance six to eight inches, four-inch spark gap, current about 3 milliampères, penetration power equal to 4 millimeters of aluminum. The animals were either killed by being opened under the influence of chloroform or were allowed to die spontaneously. In both cases the organs were removed from the body while warm and fixed at once in a saturated solution of mercuric chloride or in Flemming's solution. In a few cases in which the animal was not seen at death, the organs were fixed in a 4 per cent. solution of formaldehyde. With the exception of that fixed in Flemming's solution, all the tissues were embedded in paraffin and stained with various stains, hematoxylin and eosin being chiefly used.

Experiment 1.—White mouse exposed one-half hour. No apparent effects from the exposure. Killed at once. Autopsy appearances negative. The microscopic examination showed nuclear fragmentation of lymphocytes in the spleen. Very slight changes were found in the nuclei of the renal epithelium, consisting of a slight swelling and vacuolation of the nucleus, the chromatin particles being somewhat more compactly clumped. On the whole these changes were so slight as easily to escape notice, and would not ordinarily be regarded as pathological or as due to the exposure. Only when viewed in the light of careful control comparisons was the conclusion reached that they were the result of the irradiation.

Experiment 2.—White mouse exposed as above and killed one-half hour after the exposure. The gross appearance of the kidneys was negative. The microscopic examination showed some slight changes in the renal epithelium. The spleen contained a greater number of disintegrating lymphocytes.

Experiment 3.—White mouse exposed as above. No apparent effects. Killed one hour after the exposure. No macroscopic changes in the kidneys. The microscopic examination showed numerous disintegrating lymphoid cells in the spleen. The same slight changes were found in the renal epithelium.

Experiment 4.—White mouse exposed as above, and killed an hour and a half after the exposure. No symptoms. The macroscopic appearances of the kidneys were negative. The spleen was enlarged and dark red. The microscopic examination of the spleen showed great numbers of chromatin fragments throughout the pulp and follicles. The same slight changes in the chromatin of the renal epithelium were found but appeared less marked.

Experiment 5.—White mouse exposed as above and killed two hours after exposure. No symptoms. Macroscopic appearances of kidneys negative. Marked nuclear disintegration in the spleen. Microscopic changes in the kidney same as in the preceding.

Experiment 6.—White mouse exposed as above and killed two and a half hours after exposure. No symptoms. Macroscopic and microscopic conditions in spleen and kidneys same as in the preceding.

Experiment 7.—White mouse exposed as above. No symptoms. Killed three hours and twenty minutes after exposure. Spleen red; slightly enlarged. No macroscopic changes in kidneys. The nuclei of the renal epithelium showed such slight changes as to be practically normal.

Experiment 8.—White mouse exposed as above. No symptoms. Killed four hours after. Spleen slightly enlarged. No macroscopic changes in kidneys. Microscopic picture same as in preceding, with slightly more disintegration in the spleen.

Experiment 9.—White mouse exposed as above. Four hours after exposure the animal was more quiet than normal and its eyesight was apparently impaired. Back humped. It was killed five hours after exposure. The spleen was somewhat swollen and brownish in color. No macroscopic changes in the kidneys. Microscopic examination showed slight cloudy swelling of the renal epithelium, Experiment 10.—White mouse exposed as above. Several hours after exposure became quiet, back humped, and eyesight impaired. Was killed six hours after the exposure. The macroscopic and microscopic pictures were the same as in the preceding.

Experiment 11.—White mouse exposed as above. Several hours after the exposure developed the same symptoms as in the preceding. Was killed seven hours after exposure. The spleen was small and more brown than normal. The microscopic examination showed slight cloudy swelling of the kidney epithelium. Numerous phagocytes containing chromatin granules were scattered through the spleen pulp, and the number of lymphocytes was diminished.

Experiment 12.—White mouse exposed as above. Same symptoms. Killed eight hours after the exposure. Macroscopic and microscopic pictures the same as in the preceding.

Experiment 13.—White mouse exposed as above. Same symptoms developed a few hours after exposure. Killed fifteen hours after the exposure. Macroscopic appearances negative. Slight cloudy swelling in renal epithelium. The greater part of the disintegrated lymphoid cells in the splenic pulp and follicles were collected in large phagocytes.

Experiment 14.—White mouse exposed as above. Same symptoms developed. Was killed twenty-four hours after the exposure. Macroscopic appearances negative. Slight cloudy swelling of renal epithelium, less marked than in preceding. Fewer evidences of lymphoid disintegration. Beginning regeneration.

Experiment 15.—Young white mouse exposed for five hours. Almost immediately developed symptoms, shivering, blindness, body damp and cold, back humped, and hindquarters paretic. Became comatose and died spontaneously twelve hours after the exposure. Body very dry, shrunken, blood thick, coagulating immediately. Spleen very small and deep brown. Kidneys deep brown, small and dry. The microscopic examination showed great destruction of lymphoid cells in the spleen, lymph nodes, and bone-marrow. The kidney tubules were distended, the epithelial cells smaller than normal, but staining more deeply, their nuclei pale and vacuolated. Heavy precipitate of albumin in the tubules.

Experiment 16.—Half-grown white mouse exposed for five hours. At the end of the exposure the animal appeared very ill, back humped, eyes closed, body damp and cold, diarrhœa, paresis of hindquarters, etc. Died in twenty-four hours of slowly progressive weakness and coma. Spleen small and dark-red. Kidneys small and deep-brown. All tissues very dry. Microscopic examination showed marked destruction of lymphoid tissues. The nuclei of the renal epithelium pale and vacuolated, the cell-protoplasm diminished and granular, the tubules distended and filled with a heavy albuminous precipitate.

Experiment 17.—Young gray mouse. Exposed five hours. Same symptoms as in preceding experiment. Died of paresis and coma forty hours after exposure. Macroscopic and microscopic findings same as in the preceding.

Experiment 18.—Full-grown white mouse. Exposed five hours. Developed the same symptoms more slowly and died on the third day. Spleen very small and dark red. Kidneys small and very brown. Microscopic examination showed marked destruction of the lymphoid tissues. The renal epithelium was smaller and stained more deeply than normal and its nuclei showed vacuolation and clumping of the chromatin. The tubules were distended and filled with a granular precipitate of albumin.

Experiment 19.—Full-grown white mouse exposed for thirty-two hours and fifty-five minutes during a period of five days. Died while being exposed, developing the same symptoms as the preceding. The autopsy showed great distention of the intestines, the peritoneum was very dry, the liver small and brown, and the spleen about one-third normal size, and very firm and brown. The kidneys were diminished in size and very brown. The microscopic examination showed the renal epithelium to be smaller than normal, very granular and staining heavily with eosin. The nuclei were pale and vacuolated. The tubules were distended and filled with a heavy granular precipitate. The changes in the kidneys of this case were much more severe than in any of the preceding, and were easily recognized.

Experiment 20.—Two white rats, one full-grown white mouse, three half-grown white mice, and one young gray mouse were exposed in the same field for five hours. A medium tube was used, backed, 6 ampères through the primary of coil, four-inch parallel spark gap, about 2 milliampères through the tube; penetration equal to 16 millimeters of aluminum. All the animals showed marked symptoms within twelve hours after exposure, similar to those described above. The large white rats seemed more affected than the full-grown mouse. The young white mice died within thirty hours; the gray one forty hours after exposure. The white rats died by the eighth day; the white mouse lived until the tenth day. The autopsy appearances were negative, or the same slight changes mentioned above. In the animals dying soon after the exposure the slight nuclear changes were alone found in the kidneys; in the animals dying later the renal epithelium showed a more marked condition of cloudy swelling, the degree of the kidney lesion corresponding in general to the severity of the symptoms and the length of time between the exposure and death, the renal changes being most marked in the animals dying last. Marked destruction of the lymphoid tissues was present in all the animals, but was more extensive in the white rats.

Experiment 21.—Twelve young but full-grown rats were exposed in the same field for five hours under conditions identical with those of the last experiment. One animal was killed daily for six days; the others were allowed to die, death occurring in all cases by the eleventh day after exposure. The symptoms in all were identical with those described above, gradually increasing emaciation, paresis, and coma. The lymphoid tissues showed extensive disintegration of the lymphoid cells during the first five or six days, the chromatin granules being gathered up by phagocytes and gradually removed after this time. Immediately following the exposure very slight nuclear changes in the renal epithelium were found; in the animals dying later the kidneys were enlarged and congested. The microscopic examination showed a marked cloudy swelling.

Experiments 22 to 40.—A series of experiments was also carried out with larger animals, rabbits, etc. It is not thought necessary to give the details of these experiments, since they do not differ from those above. The results were similar. Exposures of one-half to one hour produced very minute changes in the renal epithelium apparently quickly recovering. Prolonged exposures causing symptoms (it was not possible to give exposures sufficiently prolonged to cause the death of the larger animals) were followed by a condition of cloudy swelling of the renal epithelium and an albuminuria in proportion to the degree of destruction of the lymphoid tissue. Two exceptions to this were noted in two Belgian hares, exposures of one-half and one hour respectively causing immediate albuminuria and cloudy swelling.

CONCLUSIONS.—1. From the above it will be seen that percutaneous Röntgen ray exposures of small animals for half an hour to an hour produce at once slight nuclear changes in the renal epithelium, characterized by swelling of the nucleus, vacuolation, clumping of the chromatin, and some loss of staining power. Recovery from this primary injury to the chromatin is prompt, but there follows, after six to twelve hours, a secondary kidney change characterized by albuminuria and cloudy swelling. This second change occurs during the period of phagocytosis and removal of the lymphoid detritus from the spleen, bone-marrow, and lymph nodes, and appears to be in direct proportion to the degree of lymphoid destruction. It is, of course, possible that this second kidney change is but the result of the primary disturbance of the nucleus, but the first explanation seems to me the more probable.

2. In the case of an animal exposed continuously until death occurs the renal changes are more marked, the renal cells being diminished in size, cloudy, and the tubules distended with an albuminous precipitate.

3. Continuous exposures of five hours or more are invariably fatal to small animals, death occurring within ten days following marked symptoms of paresis and coma. These symptoms also bear a definite relation to the amount of lymphoid destruction and to the kidney lesion. To what extent they are dependent

upon direct injury to the central nervous system cannot be said at the present time. The character of the symptoms suggests a primary or secondary damage to the central nervous system. The assumption of a primary injury is upheld by the fact that all small animals exposed for five hours or more became either totally or partially blind. On the other hand, the progressive development of the symptoms some days after the injury is very suggestive of an intoxication, and the character of the symptoms accords with that of poisonings due to products of protein destruction.

4. If we may make practical application of these conclusions it would seem that the destruction of great numbers of leukocytes, as occurs in the Röntgen-ray treatment of leukemia, may be dangerous to the organism, either in its action upon the central nervous system or upon the kidneys. As to the occasional irradiation of the human body it is hardly likely that any serious damage to the kidneys could result, but in the case of repeated and prolonged irradiation of the lymph nodes and spleen the possibility of renal injury should be borne in mind. Careful and repeated examinations of the urine, therefore, should be made in all such cases. In the case of preëxisting nephritis a dangerous exacerbation may be excited by irradiation.

5. It is probable that the Röntgen rays cause disturbance of the chromatin of all cells, the lymphoid cells and the epithelial cells of the testis being the most susceptible. As compared with these the renal cells are much more resistant. In a general way, then, the view is upheld that all cells capable of rapid proliferation or renewal are especially susceptible to the action of Röntgen rays.

NOTE.—Since this paper was presented before the American Röntgen-ray Society, in August, 1906, I have examined the autopsy material from a case of Hodgkin's disease treated for some time with Röntgen irradiation and have also performed an autopsy upon a case of myelogenous leukemia similarly treated. In both, but particularly in the leukemic case, the kidneys showed the same condition of "chalk infarct" and calcification described above. There can be little doubt, then, that this condition is the direct result of the treatment. Its greater extent in the two cases of myelogenous leukemia is apparently in proportion to the greater destruction of white cells. Krause and Ziegler[3] recently have practically repeated the experiments herewith detailed. These investigators were unable to discover any changes in the kidneys, after short or prolonged irradiation in mice, rabbits, guinea-pigs, rats, and dogs, that they could positively ascribe to the action of Röntgen rays. In conclusion, it may be repeated that the very minute changes caused by irradiation in the renal cells may be wholly missed unless the fixation of the tissue is perfect and careful comparison with normal renal epithelium similarly fixed is made.

[3] Fortschritte aus dem Gebiete der Röntgenstrahlen, 1906, x.